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April 28, 2014

Marcia Bailey
US EPA
Region 10

ASSISTANCE REQUESTED: External Review Comments for the Current (2012) PPRTV for Sulfolane

ENCLOSED INFORMATION: **Attachment 1**: External Peer Review Comments on the Draft Provisional Peer-Reviewed Toxicity Value (PPRTV) Manuscript for Sulfolane: Derivation of a Subchronic p-RfC; a Screening Subchronic and Chronic RfD; and a Screening Chronic RfC

If you have any questions regarding this transmission, please contact the STSC at (513) 569-7300.

Attachments (1)

cc: STSC files

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External Peer Review Comments on the Draft Provisional Peer-Reviewed Toxicity Value (PPRTV) Manuscript for Sulfolane: Derivation of a Subchronic p-RfC; a Screening Subchronic and Chronic RfD; and a Screening Chronic RfC

Contract No. EP-C-07-024
Task Order 108

Submitted to:

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Office of Research and Development
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Submitted by:

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June 28, 2011

QUALITY NARRATIVE STATEMENT

ERG selected reviewers according to selection criteria provided by EPA. EPA confirmed that the scientific credentials of the reviewers proposed by ERG fulfilled EPA's selection criteria. Reviewers conducted the review according to a charge prepared by EPA and instructions prepared by ERG. ERG checked the reviewers' written comments to ensure that each reviewer had provided a substantial response to each charge question (or that the reviewer had indicated that any question[s] not responded to was outside the reviewer's area of expertise). Since this is an independent external review, ERG did not edit the reviewers' comments in any way, but rather transmitted them unaltered to EPA.

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PEER REVIEW COMMENTS FROM

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External Peer Review Comments on the Draft Provisional Peer-Reviewed Toxicity Value (PPRTV) Manuscript for Sulfolane: Derivation of a Subchronic p-RfC; a Screening Subchronic and Chronic RfD; and a Screening Chronic RfC

Responses to Charge Questions from Dr. Mitchell Cohen

A. Provisional RfD Discussion and Derivation (screening values for a subchronic and chronic RfD are in an Appendix)

If both a subchronic and chronic RfD are developed, they may be discussed separately under each charge question or, if the same study is utilized, the values may be discussed together.

1. Organization, Clarity and Editorial Quality

Provide your opinion regarding whether this section of the PPRTV manuscript is clearly written, logically organized, concise and understandable. Provide editing or clarification corrections by reference to page and line number. Spelling and punctuation corrections may be made directly on the PPRTV manuscript, legibly and preferably in red pen. If you make such corrections, please indicate this action in your response.

This section of the Provisional Peer-Reviewed Toxicity Values for Sulfolane is logical, clear, and concise. The document provides Readers an up-to-date overview of what is known about chemical and physical characteristics of sulfolane, along with the limited info available on the: toxicokinetics of how it is handled (i.e., distribution) after exposure of animal models; (non-cancer) toxicities after (sub)chronic exposure(s) of animal models; and, any potential clastogenic/genotoxic effects. Overall, the EPA has clearly and objectively represented and synthesized the limited scientific evidence for the hazards from exposure to sulfolane.

For the most part, the conclusions reported in the document are sound. However, there are caveats that should be noted with regard to the Screening Subchronic p-RfD (Page 48) and Screening Chronic p-RfD (Page 49) values generated and why these values should be revisited/discussed further. This opinion is primarily a result of questions about appropriateness of the total level of uncertainty assigned given the status of the Principal Study at the time this PPRTV was generated.

2. Study Descriptions

Discuss whether all the studies have been adequately summarized and interpreted. Indicate any deficiencies in the description of pertinent study summaries (e.g., purity of test article, number of animals, experimental parameters, etc.). Please refer to each study by first author and date and additional designations if necessary. If necessary for clarity, make reference to page and line number in the PPRTV manuscript and/or indicate a reference directly on the manuscript (e.g., R1, 2, etc. for Comment 1, 2...). We do not require complete descriptions of non-essential supporting studies.

In general, each of the studies concerning hazards from oral exposure to sulfolane have been adequately summarized and interpreted. The information pertaining to the Principal Study is especially well spelled-out.

3. Principal and Supporting Studies

Specifically, please comment on whether the selection of the principal study(s) and supporting studies is scientifically justified, and clearly and objectively described in the PPRTV manuscript. Provide information that supports your assessment:

- If you disagree with selection of the principal study(s), clearly state the deficiencies or reasons why said selection is inappropriate.
- If you support selection of a different principal study(s), please identify the study(s) and provide the rationale for their selection.
- If you believe that no study is adequate for deriving a value, indicate this by stating the deficiencies that preclude their potential for developing values.

Though greater confidence would be instilled had the Principal Study been peer-reviewed, all of the precautions taken by the Authors in performing the study (including ongoing measures of host para-meters [weight, weight gain, food intake, etc.] and evaluation of stability of the sulfolane in the vehicle during the exposure regimen) provide enough evidence that the study was sound and acceptable for utilization as the Principal Study.

Nevertheless, as noted in comments below (see Section 5), a major concern remains regarding the lack of reproducibility among male vs. female rats with respect to the endpoint used to generate the POD. Confidence in any POD selected would be much enhanced if a value could be obtained across both (rat) sexes with respect to any non-reproductive endpoint used to define the POD. In fact, the PPRTV does a very good job explaining why effects seen only in the males (i.e., the kidney-related changes) are not acceptable for use as the POD (see Page 14-15). This is fine; however, the question then lingers as to why a similar degree of acceptance/non-acceptance was not applied to the blood cell type-related effects seen only in the females (i.e., this is apparently acceptable for use in defining POD here).

4. Additional Studies

If you are aware of relevant information not included in the PPRTV manuscript, please provide the reference and summarize the potential importance of considering each recommended study. If available, we would appreciate copies of the documents, but this is not a requirement. Access to the Health and Environmental Research Online (HERO) database will be granted by EPA for all available supporting documentation and published scientific papers pertaining to an assigned chemical.

The literature on health effects of sulfolane is extremely limited. Thus, there are no other sources of relevant information that could be suggested for inclusion in this PPRTV or for use by the EPA in determination of NOAEL, LOAEL, p-RfD, etc. values for this agent.

5. Toxicity Values

Discuss the appropriateness of the derived provisional value.

- Please comment on whether the selection of the critical effect has been scientifically justified and is clearly and objectively described in the PPRTV manuscript.

The use of changes in leukocyte types (in the female rats only) is an appropriate variable to define the critical effect(s) in the 2001 Huntington Life Sciences (Principal) study. The non-use of kidney-associated changes (in the male rats only) as the critical effect is well justified by the EPA. Still,it would have been optimal had the critical effect selected been one that was encountered by both rat sexes; there is nothing in the PPRTV review of this 2001 study that suggests such an occurrence.

- Comment on the selection of the point of departure (POD) and method of determination. The POD for the RfD cannot always be determined by a simple comparison of nominal exposure levels, given as ppm, (in food or drinking water) across studies, as food consumption and other factors may vary considerably.

The fact that there were multiple (4) doses (non-0; utilizing 4-fold increases each time) used in the principal study(s), the POD selection and the determination of any LOAEL/NOAEL by the EPA was proper. The only concern deals with the lack of reproducibility among the male rats vs. the females with respect to the endpoint used to generate the POD.

- Determine whether the correct exposure level has been selected as the POD. If appropriate, include comments on use/non-use of the BMD software, including selection of model and fit.

As noted above, the POD selection and determination of a LOAEL/NOAEL by the EPA was proper. Similarly, the choice to not employ a BMR/BMD value was proper given the information provided in the PPRTV (Pages 46-47).

- Please identify and provide rationale for any alternative approaches for the determination of the POD, and explain why such approaches are preferred to U.S. EPA's approach.

No approaches are preferable to that used by the US EPA; however, confidence in the POD would be much-enhanced if a value could be obtained across both sexes of rats with respect to any endpoint used to define the POD (see above).

- Determine whether all relevant NOAELs, LOAELs or BMDLs are expressed in terms of mg compound per kg body weight per day (mg/kg-day) and that food/water consumption factors are specified and reasonable for the animal species and gender and study type (e.g., chronic, subchronic, developmental).

As described in the PPRTV, the Principal Study took all appropriate steps to ensure that the values the EPA ultimately used to generate LOAEL/NOAEL levels were correct. This included ongoing measures of food/water intake, stability of sulfolane in vehicle, measures of body weight, etc. over the course of the entire 13-wk exposure period.

- For gavage administration, determine whether the dose levels have been adjusted for treatment schedule (e.g., 5 days per week) if applicable.

N/A

- Check all calculations, especially the dosimetric calculations, and indicate your findings.

Without specific measures of weekly water consumption per rat being provided in the PPRTV – but taking into account any exposure-related alterations in body weight gain/food conversion efficiency – the dosimetric calculations provided by the Authors of the Principal Study will have to be accepted at face value (i.e., 2.1 - 131.7 mg/kg•d for males and 2.9 - 191.1 mg/kg•d for females). If there is information available that has not been supplied regarding the ml/d (or wk) for each rat, this would be helpful for inclusion in the PPRTV so total dose (mg sulfolane) can be calculated independently to verify the study's reported values. Given these constraints about certitude of the POD/NOAEL value, and a tentative acceptance of the levels of uncertainty applied (see Section 6 below) by the EPA, the Screening Subchronic p-RfD (Page 48) and Chronic p-RfD (Page 49) values are correctly calculated.

- Verify that the units used in the calculations are correct and indicate your conclusions.

All units used in the calculations are correct.

6. Uncertainty and Confidence

Are the uncertainty factors scientifically justified and clearly and objectively described in the document? Are there other uncertainties associated with the assessment, and have they been adequately characterized?

The UFs utilized (Pages 48 and 49) are proper and appropriate for these calculations. However, due to the non-peer-reviewed status of the Principal Study, an additional factor of 10 would be appropriate to use until that study is deemed appropriate for publication by a panel of peer reviewers.

- Indicate any change in the uncertainty factors that you recommend and explain why.

An additional factor of 10 would be appropriate to use until the Principal Study is deemed appropriate for publication by a panel of peer reviewers.

- Provide your supported opinion on the determination of "Confidence" statements.

N/A

7. U.S. EPA Methodology

Discuss the assessment's adherence to EPA's risk assessment methodologies, and comment, in particular, on departures from guidance and whether any departures are reasonable and adequately supported. Considerations include selection of critical studies, endpoints, relevant toxicokinetic treatments, etc. Regarding screening values (provided in the Appendix), which may deviate from standard methodology, comment on the reasonableness of these deviations for the limited use as prescribed in the text.

There are no issues raised with respect to the assessment's adherence to EPA risk assessment methodologies or any departures from guidance. The: choices to generate/not generate values (e.g., NOAEL, LOAEL RfD, p-RfD); considerations about selection of critical studies, endpoints, relevent treatments; and, reasonableness of any deviations (assumes specific reference to generated screening value as opposed to standard [provisional] value). as stated in text appear *reasonable*/*supported*.

8. Other Comments and Information on the RfD

Provide any other suggestions for improving the scientific justification, clarity and objectivity of the assessment, indicate whether there are any other scientific considerations to address that will substantially improve the quality of the PPRTV manuscript and provide references to any additional information you believe to be critical.

Based on the information available in the given studies, there are no suggestions for improving the scientific justification, clarity, and objectivity of the assessment in this PPRTV. The quality of the PPRTV manuscript is good considering the limited info available in the literature. It is hoped that the Principal Study will reach a successful status upon peer review such that it may be used to upgrade the proposed value in this document from a screening level one to a provisional value.

B. Provisional RfC Discussion and Derivation (value derived for a subchronic p-RfC; and a screening value for a chronic RfC is in the Appendix)

If both a subchronic and chronic RfC are developed, they may be discussed separately under each charge question or, if the same study is utilized, the values may be discussed together.

9. Organization, Clarity and Editorial Quality

Provide your opinion regarding whether this section of the PPRTV manuscript is clearly written, logically organized, concise and understandable. Provide editing or clarification corrections by reference to page and line number. Spelling and punctuation corrections may be made directly on the PPRTV manuscript, legibly and preferably in red pen. If you make such corrections, please indicate this action in your response.

This portion of the *Provisional Peer-Reviewed Toxicity Values for Sulfolane* is logical, clear, and concise. The document provides Readers an up-to-date overview of the limited info available on the toxicities after (subchronic/ chronic) inhalation exposure(s) of the various animal models. Overall, the EPA has clearly and objectively represented and synthesized the limited scientific evidence for the hazards from exposure to sulfolane. For the most part, the conclusions reported are sound. However, there are caveats that should be

noted with regard to the Screening Chronic p-RfC (Page 49-50) values generated and why these values should be revisited/discussed further. This opinion is primarily a result of questions about justification of the choice Principal Study at the time this PPRTV was generated.

10. Study Descriptions

Discuss whether all the studies have been, adequately summarized and interpreted. Indicate any deficiencies in the description of pertinent study summaries (e.g., purity of test article, number of animals, experimental parameters, etc.). Please refer to each study by first author and date and additional designations if necessary. If necessary for clarity, make reference to page and line number in the PPRTV manuscript and/or indicate a reference directly on the PPRTV manuscript, e.g., (R1, 2, etc. for Comment 1, 2...). We do not require complete descriptions of non-essential supporting studies.

In general, each of the studies concerning hazards from inhalation exposures to sulfolane have been adequately summarized and interpreted.

11. Principal and Supporting Studies

Specifically, please comment on whether the selection of the principal study(s) and supporting studies is scientifically justified, and clearly and objectively described in the PPRTV manuscript. Provide information that supports this assessment.

- If you disagree with selection of the principal study(s), clearly state the deficiencies or reasons why said selection is inappropriate.
- If you support selection of a different principal study(s), please identify the study(s) and provide the rationale for their selection.
- If you believe that no study is adequate for deriving a value, indicate this by stating the deficiencies that preclude their potential for developing values.

The selection of the Andersen et al. (1977f) work as the Principal Study is not well justified. It seems this choice among the various Andersen studies was to use the one that resulted in the lowest NOAEL value. This is fine and, toxicologically, affords the most responsible approach, i.e., limit of permissible exposures is minimized. However, as the outcomes in the Andersen et al. (1977b) study with rats yield the same NOAEL and utilized more animals at each dose than in the 1977f study, it is not clear why this is not the Principal Study. Further, the 1977f study has such a clear dividing point between no effect vs. maximal effect (i.e., lethality), it is questionable if this is a good choice for Principal Study. Lastly, it is not clear why the selected 1977f study is going to be used to generate a screening chronic provisional p-RfC, if: (1) not all the hosts were exposed for the full 90-95 d period and secondly and (2) for the earlier p-RfD analyses, an exposure of 13-wk was deemed useful for sub-chronic and chronic outcomes.

Note: as stated on Page 25), in the 1977b study, the NOAEL is the 'highest concentration tested in the study that had no observed adverse effects at all concentrations". This is a badly constructed circular statement; if the clause 'at all concentrations' is deleted, it would make sense. This Reviewer wonders if this sentence - and the fact that the NOAEL is the same as the highest dose tested - was the basis for non-selection of this work as Principal Study.

Bottom line: better justification needs to be provided in any revised PPRTV for selection of Andersen et al.

(1977f) as Principal Study for determination of the Screening Chronic Provisional RfC (p-RfC).

12. Additional Studies

If you are aware of relevant information not included in the PPRTV manuscript, please provide the reference and summarize the potential importance of considering each recommended study. If available, we would appreciate copies of the documents, but this is not a requirement. Access to the Health and Environmental Research Online (HERO) database will be granted by EPA for all available supporting documentation and published scientific papers pertaining to an assigned chemical.

The literature on health effects of sulfolane is extremely limited. Thus, no other sources of relevant information could be suggested for inclusion in this PPRTV or for use by the EPA in determination of NOAEL, LOAEL, p-RfC, etc. values for this agent.

13. Toxicity Values

Discuss the appropriateness of the derived provisional value.

- Please comment on whether the selection of the critical effect has been scientifically justified and is clearly and objectively described in the PPRTV manuscript.

The use of lethality and indices of 'aggression' (and, apparently, 'by-stander' post-mortem indices of pulmonary toxicity) as endpoints for determination of a POD and the corresponding NOAEL in this study are not particularly well justified. As noted above, at least in the 1977b study, other non-lethal and non-behavioral endpoints were assessed.

- Comment on the selection of the point of departure (POD) and method of determination. The POD for the RfC cannot be determined by a simple comparison of nominal exposure levels across studies (i.e., actual exposure concentrations as ppm or mg/m3), as exposure protocols and dosimetry adjustments may vary considerably. The only directly comparable metric is the duration-adjusted human-equivalent concentration (HEC).

See above comment.

- Determine whether the correct exposure level has been selected as the POD. If appropriate, include comments on use/non-use of the BMD software, including selection of model and fit.

See above comment.

- Please identify and provide rationale for any alternative approaches for the determination of the POD, and explain why such approaches are preferred to U.S. EPA's approach.

Given the selection of Andersen et al. (1977f) as the Principal Study, the design of that study constrains any suggestions/rationale for alternative approaches for use by the EPA in this matter.

- Determine whether all relevant NOAELs, LOAELs or BMDLs are expressed as HECs, that the RGDR or RDDR models are correctly specified and that all model parameter values are given and correct.

Adequate proper justification has been provided in the PPRTV (Page 22) as to why the doses used in the inhalation studies are not converted to HECs. Instead, dosimetric adjustments were correctly made for continuous duration ($CONC_{ADJ}$) exposures.

- Check all calculations, especially the dosimetric calculations and indicate your findings.

All calculations are correct (see above in re $CONC_{ADJ}$/ $NOAEL_{ADJ}$).

- Verify that the units used in the calculations are correct and indicate your conclusions.

All units are correct.

14. Uncertainty and Confidence

Are the uncertainty factors scientifically justified and clearly and objectively described in the document? Are there other uncertainties associated with the assessment, and have they been adequately characterized?

The UFs utilized (Page 50) are proper and appropriate for these calculations. However, due to the very small sample sizes/treatment group and lack of any control (unless it is deemed that lack of effects in the lower doses is somehow equatable to a 'control') in this Principal Study, additional cautionary UFs (this Reviewer is uncertain as to how one would make this classification) would be appropriate to use.

- Indicate any change in the uncertainty factors that you recommend and explain why.

See above.

- Provide your supported opinion on the determination of "Confidence" statements.-

N/A

15. U.S. EPA Methodology

Discuss the assessment's adherence to EPA's risk assessment methodologies, and comment, in particular, on departures from guidance and whether any departures are *reasonable* and *adequately supported.* Considerations include selection of critical studies, endpoints, relevant toxicokinetic treatments, etc. Regarding screening values (provided in the Appendix), which may deviate from standard methodology, comment on the reasonableness of these deviations for the limited use as prescribed in the text.

There are no issues raised with respect to the assessment's adherence to EPA risk assessment methodologies or any departures from guidance. The: choices to generate/not generate values (e.g., NOAEL, LOAEL, RfC, p-RfC); relevant treatments; and, reasonableness of any deviations for limited use as prescribed in the text (assumes this is in specific reference to generation of screening value as opposed to standard [provisional] toxicity value) as stated in text appear reasonable and adequately supported. The only issue of concern is considerations about the selection of the critical studies and determinative endpoints; this Reviewer has expounded upon these concerns in multiple places above in the p-RfC portion of this review.

16. Other Comments and Information on the Reference Concentration

Provide any other suggestions for improving the scientific justification, clarity and objectivity of the assessment, indicate whether there is any other scientific considerations to address that will substantially improve the quality of the PPRTV manuscript and provide references to any additional information you believe to be critical.

Based on the information available in the given studies, there are no suggestions for improving the clarity and objectivity of the assessment in this PPRTV. The quality of the PPRTV manuscript is good considering the limited info on sulfolane available in the literature. It is hoped that justification for the Principal Study will be made much clearer in any revision to this document so that it may be more readily accepted as the source used to generate the proposed screening value.

C. Cancer Oral Slope Factor (OSF) (no value derived)

17. No Value Question

Do you agree with EPA’s decision not to develop a value in this document for the cancer oral slope factor? If so, why? If you do not agree with the decision, please give a detailed response as to why EPA should have developed a cancer oral slope factor value.

Yes. The lack of data available in the literature makes the choice NOT to develop a value in this document prudent. If, and when, relevant information becomes available to the EPA and the rest of the scientific community, this issue of a cancer OSF can and should be revisited.

D. Cancer Inhalation Unit Risk (IUR) (no value derived)

18. No Value Question

Do you agree with EPA's decision not to develop a value in this document for the cancer inhalation unit risk? If so, why? If you do not agree with the decision, please give a detailed response as to why EPA should have developed a cancer inhalation unit risk value.

Yes. Again, and as noted in the response above, the lack of data available in the literature makes the choice NOT to develop a cancer IUR value here prudent. If, and when, relevant information becomes available to the EPA and the rest of the scientific community regarding inhalation exposures (animal model or occupational setting, with all necessary information on exposure-related issues [concen-trations, lengths of exposures, proper controls, etc.), then the issue of a cancer IUR (provisional in nature or not) can and must be revisited.

PEER REVIEW COMMENTS FROM

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External Peer Review Comments on the Draft Provisional Peer-Reviewed Toxicity Value (PPRTV) Manuscript for Sulfolane: Derivation of a Subchronic p-RfC; a Screening Subchronic and Chronic RfD; and a Screening Chronic RfC

Responses to Charge Questions from Dr. Brent Finley

A. Provisional RfD Discussion and Derivation (screening values for a subchronic and chronic RfD are in an Appendix)

If both a subchronic and chronic RfD are developed, they may be discussed separately under each charge question or, if the same study is utilized, the values may be discussed together.

1. Organization, Clarity and Editorial Quality

Provide your opinion regarding whether this section of the PPRTV manuscript is clearly written, logically organized, concise and understandable. Provide editing or clarification corrections by reference to page and line number. Spelling and punctuation corrections may be made directly on the PPRTV manuscript, legibly and preferably in red pen. If you make such corrections, please indicate this action in your response.

The PPRTV manuscript is clearly written; I didn't see any spelling or punctuation errors.

2. Study Descriptions

Discuss whether all the studies have been adequately summarized and interpreted. Indicate any deficiencies in the description of pertinent study summaries (e.g., purity of test article, number of animals, experimental parameters, etc.). Please refer to each study by first author and date and additional designations if necessary. If necessary for clarity, make reference to page and line number in the PPRTV manuscript and/or indicate a reference directly on the manuscript (e.g., R1, 2, etc. for Comment 1, 2...). We do not require complete descriptions of non-essential supporting studies.

All of the studies have been adequately summarized. The summary tables were very helpful.

3. Principal and Supporting Studies

Specifically, please comment on whether the selection of the principal study(s) and supporting studies is scientifically justified, and clearly and objectively described in the PPRTV manuscript. Provide information that supports your assessment:

- If you disagree with selection of the principal study(s), clearly state the deficiencies or reasons why said selection is inappropriate.
- If you support selection of a different principal study(s), please identify the study(s) and provide the rationale for their selection.
- If you believe that no study is adequate for deriving a value, indicate this by stating the deficiencies that preclude their potential for developing values.

I agree with the selection of the Huntingdon study as the most appropriate basis of a screening oral RfD; I agree that the study of Zhu et al (1987c) should NOT be used as the principal study, even though it reported a lower NOAEL, due to the study deficiencies that are clearly articulated in the PPRTV document.

4. Additional Studies

If you are aware of relevant information not included in the PPRTV manuscript, please provide the reference and summarize the potential importance of considering each recommended study. If available, we would appreciate copies of the documents, but this is not a requirement. Access to the Health and Environmental Research Online (HERO) database will be granted by EPA for all available supporting documentation and published scientific papers pertaining to an assigned chemical.

I conducted an independent search and did not find any other relevant studies

5. Toxicity Values

Discuss the appropriateness of the derived provisional value.

- Please comment on whether the selection of the critical effect has been scientifically justified and is clearly and objectively described in the PPRTV manuscript.

The critical effect (decreased blood cell counts in female rats) was properly chosen.

- Comment on the selection of the point of departure (POD) and method of determination. The POD for the RfD cannot always be determined by a simple comparison of nominal exposure levels, given as ppm, (in food or drinking water) across studies, as food consumption and other factors may vary considerably.

The POD of 2.9 mg/kg-day (the NOAEL) was properly chosen.

- Determine whether the correct exposure level has been selected as the POD. If appropriate, include comments on use/non-use of the BMD software, including selection of model and fit.

Based on the data presented in the original study, the correct exposure level was chosen as the POD. BMD analyses were not feasible in this case.

- Please identify and provide rationale for any alternative approaches for the determination of the POD, and explain why such approaches are preferred to U.S. EPA's approach.

I don't know of any alternative approaches superior to that presented in the PPRTV document.

- Determine whether all relevant NOAELs, LOAELs or BMDLs are expressed in terms of mg compound per kg body weight per day (mg/kg-day) and that food/water consumption factors are specified and reasonable for the animal species and gender and study type (e.g., chronic, subchronic, developmental).

The NOAEL is properly expressed as mg/kg-day.

- For gavage administration, determine whether the dose levels have been adjusted for treatment schedule (e.g., 5 days per week) if applicable.

N/A

- Check all calculations, especially the dosimetric calculations, and indicate your findings.

The calculations are correct.

- Verify that the units used in the calculations are correct and indicate your conclusions.

The units are correct.

6. Uncertainty and Confidence

Are the uncertainty factors scientifically justified and clearly and objectively described in the document? Are there other uncertainties associated with the assessment, and have they been adequately characterized?

I thought the UFs were clearly characterized.

- Indicate any change in the uncertainty factors that you recommend and explain why.

I agree with the aggregate UFs of 300 and 3,000

- Provide your supported opinion on the determination of "Confidence" statements.

See my comment to #8 below

7. U.S. EPA Methodology

Discuss the assessment's adherence to EPA's risk assessment methodologies, and comment, in particular, on departures from guidance and whether any departures are *reasonable* and *adequately supported*. Considerations include selection of critical studies, endpoints, relevant toxicokinetic treatments, etc. Regarding screening values (provided in the Appendix), which may deviate from standard methodology, comment on the reasonableness of these deviations for the limited use as prescribed in the text.

The methodology used here is standard EPA methodology for setting RfDs.

8. Other Comments and Information on the RfD

Provide any other suggestions for improving the scientific justification, clarity and objectivity of the assessment, indicate whether there are any other scientific considerations to address that will substantially improve the quality of the PPRTV manuscript and provide references to any additional information you believe to be critical.

I take issue with the view that the sulfolane RfDs must be relegated to “screening values” simply because the Huntingdon study was not “peer-reviewed” or “published”. First, I’m not sure it is accurate to say it wasn’t peer-reviewed. Certainly there was some internal peer review and currently it is being reviewed by me and others who are evaluating the PPRTV document. Second, let’s face it, ALL of the other oral studies were “peer reviewed” and even published in peer reviewed journals yet they were severely flawed. Hence, the statement that the screening values have limitations and may be only “of limited use”, when the underlying Huntingdon study appears to be a high quality study in every way, just doesn’t seem appropriate. I would think the EPA staff who developed this document should be able to make the call on this (as to whether this is or isn’t a quality study that can be used to set a provisional value, regardless of the publication status). Still, I understand this is probably a general policy decision…but I think the decision should be on a case by case basis.

B. Provisional RfC Discussion and Derivation (value derived for a subchronic p-RfC; and a screening value for a chronic RfC is in the Appendix)

If both a subchronic and chronic RfC are developed, they may be discussed separately under each charge question or, if the same study is utilized, the values may be discussed together.

9. Organization, Clarity and Editorial Quality

Provide your opinion regarding whether this section of the PPRTV manuscript is clearly written, logically organized, concise and understandable. Provide editing or clarification corrections by reference to page and line number. Spelling and punctuation corrections may be made directly on the PPRTV manuscript, legibly and preferably in red pen. If you make such corrections, please indicate this action in your response.

This section of the PPRTV document was very clear and concise.

10. Study Descriptions

Discuss whether all the studies have been, adequately summarized and interpreted. Indicate any deficiencies in the description of pertinent study summaries (e.g., purity of test article, number of animals, experimental parameters, etc.). Please refer to each study by first author and date and additional designations if necessary. If necessary for clarity, make reference to page and line number in the PPRTV manuscript and/or indicate a reference directly on the PPRTV manuscript, e.g., (R1, 2, etc. for Comment 1, 2...). We do not require complete descriptions of non-essential supporting studies.

I found the studies to be described in adequate detail and I liked the way the different species from Andersen et al (1977) were addressed separately.

11. Principal and Supporting Studies

Specifically, please comment on whether the selection of the principal study(s) and supporting studies is scientifically justified, and clearly and objectively described in the PPRTV manuscript. Provide information that supports this assessment.

- If you disagree with selection of the principal study(s), clearly state the deficiencies or reasons why said selection is inappropriate.
- If you support selection of a different principal study(s), please identify the study(s) and provide the rationale for their selection.
- If you believe that no study is adequate for deriving a value, indicate this by stating the deficiencies that preclude their potential for developing values.

There’s no question that Andersen et al should be the principal study.

12. Additional Studies

If you are aware of relevant information not included in the PPRTV manuscript, please provide the reference and summarize the potential importance of considering each recommended study. If available, we would appreciate copies of the documents, but this is not a requirement. Access to the Health and Environmental Research Online (HERO) database will be granted by EPA for all available supporting documentation and published scientific papers pertaining to an assigned chemical.

I am not aware of any other relevant inhalation studies with sulfolane.

13. Toxicity Values

Discuss the appropriateness of the derived provisional value.

- Please comment on whether the selection of the critical effect has been scientifically justified and is clearly and objectively described in the PPRTV manuscript.

The critical effect (NOAEL in dogs) was chosen appropriately

- Comment on the selection of the point of departure (POD) and method of determination. The POD for the RfC cannot be determined by a simple comparison of nominal exposure levels across studies (i.e., actual exposure concentrations as ppm or mg/m3), as exposure protocols and dosimetry adjustments may vary considerably. The only directly comparable metric is the duration-adjusted human-equivalent concentration (HEC).

The POD (NOAEL of 20 mg/m3) was chosen appropriately; derivation of an HEC was not possible due to lack of particle size information

- Determine whether the correct exposure level has been selected as the POD. If appropriate, include comments on use/non-use of the BMD software, including selection of model and fit.

The correct exposure level (and species) was chosen; BMD wasn't used because there was no dose response relationship to model.

- Please identify and provide rationale for any alternative approaches for the determination of the POD, and explain why such approaches are preferred to U.S. EPA's approach.

I don't know of any superior, alternative techniques.

- Determine whether all relevant NOAELs, LOAELs or BMDLs are expressed as HECs, that the RGDR or RDDR models are correctly specified and that all model parameter values are given and correct.

As noted above, the NOAEL was not converted to an HEC due to lack of information.

- Check all calculations, especially the dosimetric calculations and indicate your findings.

The dosimetric adjustments on page 42 were done correctly.

- Verify that the units used in the calculations are correct and indicate your conclusions.

The units in the calculations are correct.

14. Uncertainty and Confidence

Are the uncertainty factors scientifically justified and clearly and objectively described in the document? Are there other uncertainties associated with the assessment, and have they been adequately characterized?

I think the UFs for the provisional subchronic and screening chronic RfC were properly chosen and characterized

- Indicate any change in the uncertainty factors that you recommend and explain why.

N/A

- Provide your supported opinion on the determination of "Confidence" statements.-

Given the lack of particle size information, and the fact that there is only one study (although it does have several species), I agree that the confidence in the subchronic RfC should be “low”.

15. U.S. EPA Methodology

Discuss the assessment's adherence to EPA's risk assessment methodologies, and comment, in particular, on departures from guidance and whether any departures are *reasonable* and *adequately supported.* Considerations include selection of critical studies, endpoints, relevant toxicokinetic treatments, etc. Regarding screening values (provided in the Appendix), which may deviate from standard methodology, comment on the reasonableness of these deviations for the limited use as prescribed in the text.

The methods used here conform to standard EPA methodology.

16. Other Comments and Information on the Reference Concentration

Provide any other suggestions for improving the scientific justification, clarity and objectivity of the assessment, indicate whether there is any other scientific considerations to address that will substantially improve the quality of the PPRTV manuscript and provide references to any additional information you believe to be critical.

None

C. Cancer Oral Slope Factor (OSF) (no value derived)

17. No Value Question

Do you agree with EPA's decision not to develop a value in this document for the cancer oral slope factor? If so, why? If you do not agree with the decision, please give a detailed response as to why EPA should have developed a cancer oral slope factor value.

Yes I agree because there are no relevant oral data.

D. Cancer Inhalation Unit Risk (IUR) (no value derived)

18. No Value Question

Do you agree with EPA's decision not to develop a value in this document for the cancer inhalation unit risk? If so, why? If you do not agree with the decision, please give a detailed response as to why EPA should have developed a cancer inhalation unit risk value.

Yes, I agree because there are no relevant inhalation data.

PEER REVIEW COMMENTS FROM

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External Peer Review Comments on the Draft Provisional Peer-Reviewed Toxicity Value (PPRTV) Manuscript for Sulfolane: Derivation of a Subchronic p-RfC; a Screening Subchronic and Chronic RfD; and a Screening Chronic RfC

Responses to Charge Questions from Dr. Lisa Kamendulis

A. Provisional RfD Discussion and Derivation (screening values for a subchronic and chronic RfD are in an Appendix)

If both a subchronic and chronic RfD are developed, they may be discussed separately under each charge question or, if the same study is utilized, the values may be discussed together.

1. Organization, Clarity and Editorial Quality

Provide your opinion regarding whether this section of the PPRTV manuscript is clearly written, logically organized, concise and understandable. Provide editing or clarification corrections by reference to page and line number. Spelling and punctuation corrections may be made directly on the PPRTV manuscript, legibly and preferably in red pen. If you make such corrections, please indicate this action in your response.

The document was well organized and presented the available information for the derivation of subchronic and chronic RfDs and RfCs (screening and/or provisional) for sulfolane in a clear and concise manner.

Only a couple of minor suggestions are offered to clarify the document. Page 14 line 20 “statistically significantly different” - this is redundant by definition – statistically different would suffice. Page 24 lines 14-15 “stastically nonsignificant decrease” by definition, if the difference was non-significant, that it cannot be of statistical significance. Suggest modifying this sentence.

Page 44 Table 9. Define the meaning of “NA”

I suggest that a notation be placed in the footers for the uncertainty factor tables that defines the subscript for the uncertainty factors. Readers of this document may not be familiar with the uncertainty factor categories.

2. Study Descriptions

Discuss whether all the studies have been adequately summarized and interpreted. Indicate any deficiencies in the description of pertinent study summaries (e.g., purity of test article, number of animals, experimental parameters, etc.). Please refer to each study by first author and date and additional designations if necessary. If necessary for clarity, make reference to page and line number in the PPRTV manuscript and/or indicate a reference directly on the manuscript (e.g., R1, 2, etc. for Comment 1, 2...). We do not require complete descriptions of non-essential supporting studies.

The studies describing the sub-chronic and chronic effects of sulfolane were very well described. The findings of each study were generally clearly and accurately depicted in this document. The summaries contained descriptions of pertinent information and/or clearly indicated information that was not available or reported.

3. Principal and Supporting Studies

Specifically, please comment on whether the selection of the principal study(s) and supporting studies is scientifically justified, and clearly and objectively described in the PPRTV manuscript. Provide information that supports your assessment:

- If you disagree with selection of the principal study(s), clearly state the deficiencies or reasons why said selection is inappropriate.
- If you support selection of a different principal study(s), please identify the study(s) and provide the rationale for their selection.
- If you believe that no study is adequate for deriving a value, indicate this by stating the deficiencies that preclude their potential for developing values.

I agree with the selection of the Huntington Life Sciences (2001) study as the principal study for deriving RfD values for sulfolane. While this study was conducted under GLP guidelines, it has yet to be peer-reviewed. This is clearly stated in the document and it is also clearly and correctly used to derive screening values for sulfolane (rather than a p-RfD)..

4. Additional Studies

If you are aware of relevant information not included in the PPRTV manuscript, please provide the reference and summarize the potential importance of considering each recommended study. If available, we would appreciate copies of the documents, but this is not a requirement. Access to the Health and Environmental Research Online (HERO) database will be granted by EPA for all available supporting documentation and published scientific papers pertaining to an assigned chemical.

I am not aware or could identify additional studies that were more appropriate, or could be used for deriving a subchronic p-RfDs for sulfolane.

5. Toxicity Values

Discuss the appropriateness of the derived provisional value.

- Please comment on whether the selection of the critical effect has been scientifically justified and is clearly and objectively described in the PPRTV manuscript.

I agree with the assessment that decreases in white blood cell counts in female rats was the most sensitive toxic endpoint for oral effects of sulfolane. This endpoint was supported in additional studies and species, and in female rats, was dose-related and statistically significant.

- Comment on the selection of the point of departure (POD) and method of determination. The POD for the RfD cannot always be determined by a simple comparison of nominal exposure levels, given as ppm, (in food or drinking water) across studies, as food consumption and other factors may vary considerably.

Due to the fact that the most scientifically justified toxic endpoint is reported in a non-peer reviewed

document, p-RfDs for solfolane could not be derived. Instead, the Huntington study (2001) was used to derive a screening p-RfD for sulfolane. BMD modeling approaches were attempted using the available data, however, the data fit poorly into all available models, as such the NOAEL was used as the POD. I agree with this approach.

- Determine whether the correct exposure level has been selected as the POD. If appropriate, include comments on use/non-use of the BMD software, including selection of model and fit.

As noted above, the NOAEL was used as the POD. This is the approapriate value to use to derive a screening value for sulfolane.

- Please identify and provide rationale for any alternative approaches for the determination of the POD, and explain why such approaches are preferred to U.S. EPA's approach.

The approach provided by the US EPA for the determination of POD is appropriate.

- Determine whether all relevant NOAELs, LOAELs or BMDLs are expressed in terms of mg compound per kg body weight per day (mg/kg-day) and that food/water consumption factors are specified and reasonable for the animal species and gender and study type (e.g., chronic, subchronic, developmental).

The NOAELs, LOAELs appeared to be appropriately expressed (mg/kg-day values reported).

- For gavage administration, determine whether the dose levels have been adjusted for treatment schedule (e.g., 5 days per week) if applicable.

N/A

- Check all calculations, especially the dosimetric calculations, and indicate your findings.

The calculations are correct

- Verify that the units used in the calculations are correct and indicate your conclusions.

The units are correct.

6. Uncertainty and Confidence

Are the uncertainty factors scientifically justified and clearly and objectively described in the document? Are there other uncertainties associated with the assessment, and have they been adequately characterized?

The uncertainty factors used for the derivation of a subchronic p-RfD for sulfolane. As mentioned in the response to question 1 above, I suggest that a notation be placed in the footers for the uncertainty factor tables that defines the subscript for the uncertainty factors to assist readers who may not be familiar with the uncertainty factor categories.

- Indicate any change in the uncertainty factors that you recommend and explain why.

No changes are suggested

- Provide your supported opinion on the determination of "Confidence" statements.

The overall confidence for the determination of screening RfDs is not reported (in tabular form as is convention for p-RfDs). It is clearly and appropriately stated that there is considerably less certainty associated with derived screening RfD values.

7. U.S. EPA Methodology

Discuss the assessment's adherence to EPA's risk assessment methodologies, and comment, in particular, on departures from guidance and whether any departures are *reasonable* and *adequately supported*. Considerations include selection of critical studies, endpoints, relevant toxicokinetic treatments, etc. Regarding screening values (provided in the Appendix), which may deviate from standard methodology, comment on the reasonableness of these deviations for the limited use as prescribed in the text.

This PPRTV for establishing screening RfDs for sulfolane appear to follow EPA’s Risk Assessment Methodologies. The dataset for deriving screening RfDs (subchronic and chronic) for sulfolane is based on a subchronic study in rats. The methodology for the screening RfD derivations are scientifically based and well described, and takes into account the appropriate uncertainty factors as well as adequately describing the uncertainty in using derived screening RfD values to assess risk/hazzard.

8. Other Comments and Information on the RfD

Provide any other suggestions for improving the scientific justification, clarity and objectivity of the assessment, indicate whether there are any other scientific considerations to address that will substantially improve the quality of the PPRTV manuscript and provide references to any additional information you believe to be critical.

No other comments are suggested.

B. Provisional RfC Discussion and Derivation (value derived for a subchronic p-RfC; and a screening value for a chronic RfC is in the Appendix)

If both a subchronic and chronic RfC are developed, they may be discussed separately under each charge question or, if the same study is utilized, the values may be discussed together.

9. Organization, Clarity and Editorial Quality

Provide your opinion regarding whether this section of the PPRTV manuscript is clearly written, logically organized, concise and understandable. Provide editing or clarification corrections by reference to page and line number. Spelling and punctuation corrections may be made directly on the PPRTV manuscript, legibly and preferably in red pen. If you make such corrections, please indicate this action in your response.

In general, the document was well organized and presented the available information for the derivation of provisional subchronic and screening chronic RfCs for sulfolane in a clear and concise manner.

10. Study Descriptions

Discuss whether all the studies have been, adequately summarized and interpreted. Indicate any deficiencies in the description of pertinent study summaries (e.g., purity of test article, number of animals, experimental parameters, etc.). Please refer to each study by first author and date and additional designations if necessary. If necessary for clarity, make reference to page and line number in the PPRTV manuscript and/or indicate a reference directly on the PPRTV manuscript, e.g., (R1, 2, etc. for Comment 1, 2...). We do not require complete descriptions of non-essential supporting studies.

Only a limited number of studies exist that describe the effects of sulfolane via inhalation exposure. All studies were clearly presented in the document. The document clearly indicated when and what limitations existed in studies.

11. Principal and Supporting Studies

Specifically, please comment on whether the selection of the principal study(s) and supporting studies is scientifically justified, and clearly and objectively described in the PPRTV manuscript. Provide information that supports this assessment.

- If you disagree with selection of the principal study(s), clearly state the deficiencies or reasons why said selection is inappropriate.
- If you support selection of a different principal study(s), please identify the study(s) and provide the rationale for their selection.
- If you believe that no study is adequate for deriving a value, indicate this by stating the deficiencies that preclude their potential for developing values.

The subchronic study by Andersen et al., 1977f was selected as the principal study for the derivation of a subchronic RfC and a screening chronic RfC for sullfolane. While the methodologies followed for deriving RfC appear to follow EPA guidelines (see next sections), this study used only a limited

number of animals per treatment group (n=1, n=1, n=2, and n=4). This is an inadequate design and I feel that this is not appropriate to use for the purposes of deriving RfC values for sulfolane. Perhaps the Andersen 1977h is a more appropriate study due to the use of larger group sizes (n=9). Similar to the Andersen 1977f study, this study did not identify a LOAEL (rather an FEL based on death) but did identify a NOAEL of 19.2 (the same as identified in the Andersen 1977f study).

12. Additional Studies

If you are aware of relevant information not included in the PPRTV manuscript, please provide the reference and summarize the potential importance of considering each recommended study. If available, we would appreciate copies of the documents, but this is not a requirement. Access to the Health and Environmental Research Online (HERO) database will be granted by EPA for all available supporting documentation and published scientific papers pertaining to an assigned chemical.

I am not aware of other studies that could be used to derive subchronic or chronic RfCs for sulfolane.

13. Toxicity Values

Discuss the appropriateness of the derived provisional value.

- Please comment on whether the selection of the critical effect has been scientifically justified and is clearly and objectively described in the PPRTV manuscript.

No effects were observed at the next lowest dose from which toxic endpoints were observed (the FEL – where severe motor seizures, convulsions, death were observed). While I am not in agreement with the selection of the Andersen 1977f study as the principal study, similar observations were recorded in the Andersen 1977h study.

- Comment on the selection of the point of departure (POD) and method of determination. The POD for the RfC cannot be determined by a simple comparison of nominal exposure levels across studies (i.e., actual exposure concentrations as ppm or mg/m3), as exposure protocols and dosimetry adjustments may vary considerably. The only directly comparable metric is the duration-adjusted human-equivalent concentration (HEC).

Since a dose-response relationship in any toxic endpoint was not observed, BMD modeling would not be able to be performed.

- Determine whether the correct exposure level has been selected as the POD. If appropriate, include comments on use/non-use of the BMD software, including selection of model and fit.

The NOAEL was used as the POD. Due to the limitations in the available datasets, this is appropriate.

- Please identify and provide rationale for any alternative approaches for the determination of the POD, and explain why such approaches are preferred to U.S. EPA's approach.

I am not aware of alternative approaches that could be used to derive screening or p-RfC values for sulfolane.

- Determine whether all relevant NOAELs, LOAELs or BMDLs are expressed as HECs, that the RGDR or RDDR models are correctly specified and that all model parameter values are given and correct.

The NOAEL values provided are correctly noted in the document.

- Check all calculations, especially the dosimetric calculations and indicate your findings.

The calculations as presented are correct (see below for comment on the use of UFs for the derivation of the screening chronic RfC).

- Verify that the units used in the calculations are correct and indicate your conclusions.

The units used in all calculations presented in the document are correct.

14. Uncertainty and Confidence

Are the uncertainty factors scientifically justified and clearly and objectively described in the document? Are there other uncertainties associated with the assessment, and have they been adequately characterized?

The UFs used for the derivation of a subchronic RfC for sulfolane are clearly and objectively described in the document. For the derivation of a screening RfC for sulfolane, a combined UF of 10,000 is applied. It is not clear why this factor was applied. Had this been the derivation of a chronic p-RfC, having a combined UF >3000 would disallow calculation of this value. It is therefore questioned whether the derivation of a chronic screening RfC is appropriate.

- Indicate any change in the uncertainty factors that you recommend and explain why.

Changes in the UF vales are not being suggested. See comment above on whether the derivation of any chronic RfC value scientifically appropriate given the limited data available.

- Provide your supported opinion on the determination of "Confidence" statements.-

I agree that overall confidence in the subchronic RfC is low. It is also clearly stated that using screening values for the characterization of risk from inhalation exposure to sulfolane is considerable lower based on an inadequate data set.

15. U.S. EPA Methodology

Discuss the assessment's adherence to EPA's risk assessment methodologies, and comment, in particular, on departures from guidance and whether any departures are *reasonable* and *adequately supported.* Considerations include selection of critical studies, endpoints, relevant toxicokinetic treatments, etc. Regarding screening values (provided in the Appendix), which may deviate from standard methodology, comment on the reasonableness of these deviations for the limited use as prescribed in the text.

This PPRTV for establishing a provisional subchronic and screening chronic RfC for sulfolane appears to follow EPA's Risk Assessment Methodologies. The methodology for the subchronic p-RfC derivations appears to be scientifically based and well described, and takes into account the appropriate uncertainty factors. See comment above on the UFs associated with the derivation of screening RfC for sulfolane.

16. Other Comments and Information on the Reference Concentration

Provide any other suggestions for improving the scientific justification, clarity and objectivity of the assessment, indicate whether there is any other scientific considerations to address that will substantially improve the quality of the PPRTV manuscript and provide references to any additional information you believe to be critical.

No other comments are suggested.

C. Cancer Oral Slope Factor (OSF) (no value derived)

17. No Value Question

Do you agree with EPA's decision not to develop a value in this document for the cancer oral slope factor? If so, why? If you do not agree with the decision, please give a detailed response as to why EPA should have developed a cancer oral slope factor value.

No carcinogenicity studies (oral or inhalation) have been performed for sulfolane. Therefore I agree with EPAs decision to not derive an oral slope factor for sulfolane.

D. Cancer Inhalation Unit Risk (IUR) (no value derived)

18. No Value Question

Do you agree with EPA's decision not to develop a value in this document for the cancer inhalation unit risk? If so, why? If you do not agree with the decision, please give a detailed response as to why EPA should have developed a cancer inhalation unit risk value.

No carcinogenicity studies (oral or inhalation) have been performed for sulfolane. Therefore I agree with EPAs decision to not derive an inhalation unit risk value for sulfolane.